L1: Entry 90 of 134 File: USPT May 20, 1997

DOCUMENT-IDENTIFIER: US 5631378 A
TITLE: Protected aminothiazolylacetic acid derivatives

Brief Summary Text (3):
The present invention relates to protected aminothiazolyl acetic acid derivatives and salts thereof, which are preparation intermediates useful for introducing a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetyl group or a 2-(2-aminothiazol-4-yl)-2-alkenoyl group into a cephem skeleton, and also to a process for the preparation thereof. The above alkoxyiminoacetyl group or alkenoyl group is a moiety common to antibiotics such as Cefmenoxime, Cefpodoxime proxetil, Cefepime, Cefpirome, Cefzopran, Cefclidine, DQ-2556 (CAS Registry No. 102253-70-3), FK-037 (CAS Registry No. 122841-12-7), E1077 (CAS Registry No.116853-25-9), and S-1108 (CAS Registry No. 105889-45-0), and the like.

Brief Summary Text (5):
Antibiotics such as Cefmenoxime, Cefpodoxime proxetil, Cefepime, Cefpirome, Cefzopran, Cefclidine, DQ-2556, FK-037 and E1077 and the like contain a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetyl group or a 2-(2-aminothiazol-4-yl)-2-alkenoyl group as a common moiety in their molecules. To obtain still higher antibacterial activities, this substituent is essential.

Brief Summary Text (13):
The present invention therefore provides a novel protected aminothiazolylacetic acid derivative (I) or a salt thereof which is useful for introducing a 2-(2-aminothiazol-4-yl)-2-alkoxyiminoacetyl group or a 2-(2-aminothiazol-4-yl)-2-alkenoyl group which is a moiety common to antibiotics such as Cefmenoxime, Cefpodoxime proxetil, Cefepime, Cefpirome, Cefzopran, Cefclidine, DQ-2556, FK-037 and E1077, and the like and also a process for the preparation thereof.

L1: Entry 76 of 134 File: USPT Nov 11, 1997

DOCUMENT-IDENTIFIER: US 5686441 A
**** See image for Certificate of Correction ****
TITLE: Penam sulfones as .beta.-lactamase inhibitors

Brief Summary Text (18):
The .beta.-lactamase inhibitors of the invention are effective in enhancing the antimicrobial activity of .beta.-lactam antibiotics, when used in combination with the .beta.-lactam antibiotic to treat a mammalian subject suffering from a bacterial infection caused by a .beta.-lactamase producing microorganism. Examples of antibiotics which can be used in combination with the compounds of the present invention are commonly used penicillins, such as amoxicillin, ampicillin, azlocillin, mezlocillin, apalcillin, hetacillin, bacampicillin, carbenicillin, sulbenicillin, ticarcillin, piperacillin, mecillinam, methicillin, ciclacillin, talampicillin, and commonly used cephalosporins, such as cephalothin, cephaloridine, cefaclor, cefadroxil, cefamandole, cefazolin, cephalexin, cephradine, cephapirin, cefuroxime, cefoxitin, cephacetrile, cefotiam, cefotaxime, cefatriazine, cefsulodin, cefoperazone, ceftizoxime, cefmenoxime, cefmetazole, cephaloglycin, cefonicid, cefodizime, cefpirome, ceftazidime, cefpiramide, ceftriaxone, cefbuperazone, and salts thereof.

CLAIMS:

11. The method of claim 8 wherein the .beta.-lactam antibiotic is selected from the group consisting of amoxicillin, ampicillin, azlocillin, mezlocillin, apalcillin, hetacillin, bacampicillin, carbenicillin, sulbenicillin, ticarcillin, piperacillin, mecillinam, methicillin, ciclacillin, talampicillin, cephalothin, cephaloridine, cefaclor, cefadroxil, cefamandole, cefazolin, cephalexin, cephradine, cephapirin, cefuroxime, cefoxitin, cephacetrile, cefotiam, cefotaxime, cefatriazine, cefsulodin, cefoperazone, ceftizoxime, cefmenoxime, cefmetazole, cephaloglycin, cefonicid, cefodizime, cefpirome, ceftazidime, cefpiramide, ceftriaxone, and cefbuperazone.

L3 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AB A stabilized pharmaceutical composition having a combined **quinupristine**/dalfopristine base and containing an at least stoichiometric amount of methanesulphonic acid or hydrochloric acid and being characterized in that its pH ranges from about 3.5 to about 5. Methods of making and using the stabilized composition are also disclosed.

AN 2000:290699 BIOSIS
DN PREV200000290699

TI Stabilized pharmaceutical compositions, with **quinupristine** and dalfopristine base and their preparation.

AU Bounine, Jean-Paul (1); Conrath, Guillaume
CS (1) Maisons Alfort France
ASSIGNEE: Rhone Poulenc Rorer S.A., Antony, France

PI US 5994338 November 30, 1999
SO Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 30, 1999) Vol. 1228, No. 5, pp. No pagination. e-file. ISSN: 0098-1133.
DT Patent
LA English

L2 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

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DT Patent
LA English

L2 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

AB The present invention relates to injectable compositions containing a **dalfopristine**/quinupristine combination comprising an aqueous solution containing the **dalfopristine**/quinopristine combination and an additive intended to avoid or reduce the intolerance effects at the site of injection.

AN 2001:366168 BIOSIS

DN PREV200100366168

TI Pharmaceutical compositions based on **dalfopristine** and on quinupristine, and preparation thereof.

AU Conrath, Guillaume (1); Vacus, Joel; Barker, Nicholas Paul

CS (1) Chatenay Malabry France
ASSIGNEE: Rhone-Poulenc Rorer S.A., Antony, France

PI US 6187746 February 13, 2001

SO Official Gazette of the United States Patent and Trademark Office Patents, (Feb. 13, 2001) Vol. 1243, No. 2, pp. No Pagination. e-file.
ISSN: 0098-1133.

DT Patent

LA English

L2: Entry 5 of 8 File: USPT Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994338 A
**** See image for Certificate of Correction ****
TITLE: Stabilized pharmaceutical compositions, with quinupristine and dalfopristine base and their preparation

Abstract Text (1):
A stabilized pharmaceutical composition having a combined quinupristine/dalfopristine base and containing an at least stoichiometric amount of methanesulphonic acid or hydrochloric acid and being characterized in that its pH ranges from about 3.5 to about 5. Methods of making and using the stabilized composition are also disclosed.

Brief Summary Text (1):
The present invention relates to stabilized pharmaceutical.compositions intended for the parenteral administration of quinupristine and of dalfopristine components of Synercid.RTM..

Brief Summary Text (3):
Quinupristine, a derivative of pristinamycin I, and dalfopristine, a derivative of pristinamycin II, are the components of Synercid.RTM.: ##STR3##

Brief Summary Text (4):
Synercid.RTM. (quinupristine/dalfopristine) is an injectable 30/70 combination, the antibacterial activity of which, in particular with respect to vancomycin-resistant germs, is cited in numerous publications [The Annals of Pharmacotherapy, 29, 1022-1026 (1995); Microbial Drug Resistance, 1, 223-234 (1995)].

Brief Summary Text (5):
The solubilization of the isolated components quinupristine or dalfopristine can be obtained in the salt state.

Brief Summary Text (6):
However, the fact of having to dissolve a combination poses numerous problems, in particular the problem of finding a salifying agent capable of being suitable for each of the components. Moreover, it is necessary to make sure that the pharmaceutical composition exhibits a stability such that the dosage of active principle initially fixed is constant during the lifetime of the medicament. The constitution of stabilized pharmaceutical compositions comprising the quinupristine/dalfopristine combination, the stability of solutions and/or of lyophilisates prepared from solutions, have posed serious problems of preparation which can bring into question the possibility of using them to make a medicament which can be stored and thus marketed. This is due in particular to the significant appearance of degradation impurities.

Brief Summary Text (7):
It has now been found that it is possible to stabilize pharmaceutical compositions comprising the quinupristine/dalfopristine combination by use of at least stoichiometric amounts of methanesulphonic acid or of hydrochloric acid, at a pH within the range [3.5; 5]. Thus, solutions based on methanesulphonic or hydrochloric acid having a pH in the range [3.5; 5] are sufficiently stable for the production of an industrial preparation and result, depending on the situation, in lyophilisates, in reconstituted solutions after lyophilization and/or in frozen solutions which are

, stable and thus storable with a view to marketing and/or a therapeutic use.

Brief Summary Text (9):
dalfopristine and quinupristine; methanesulphonic or hydrochloric acid, in an at least stoichiometric amount with respect to the sum of the dalfopristine and of the quinupristine introduced;

Brief Summary Text (17):
The stabilized pharmaceutical compositions according to the invention preferably contain concentrations of quinupristine/dalfopristine active principle of between 5 and 250 mg/ml or, in the case of a lyophilisate, in proportions of between 5 and 95%, a proportion of 20 to 90% being more preferred. It is clearly understood that stabilized pharmaceutical compositions of lower concentration can also be produced and clinically used; these solutions also come within the scope of the present invention.

Brief Summary Text (18):
The amount of acid depends on the amount of dalfopristine and quinupristine. It is determined so as to have at least stoichiometric proportions and in such a way as to obtain solutions for which the pH is within the range [3.5; 5].

Brief Summary Text (24):
The stabilized pharmaceutical compositions according to the invention are prepared by simultaneously or successively dissolving quinupristine, dalfopristine, methanesulphonic acid or hydrochloric acid in water and then adjusting the pH in the range [3.5; 5] and/or adding an isotonizing agent and/or adding other pharmaceutically acceptable adjuvants and, if appropriate, lyophilizing and/or freezing.

Brief Summary Text (25):
According to a preferred aspect, the compositions according to the invention are prepared by dissolving the quinupristine component and then the dalfopristine component in water acidified by methanesulphonic acid or hydrochloric acid, followed, if appropriate, by the adjustment of the pH in the range [3.5; 5] and/or by the addition of an isotonizing agent and/or of other pharmaceutically acceptable adjuvants. They are, if appropriate, lyophilized and/or frozen.

Detailed Description Text (3):
One litre of a 125 mg/ml solution of quinupristine/dalfopristine (30/70), salified by methanesulphonic acid (.apprxeq.16.7 mg/ml), at a pH of 4.75, is prepared by introducing 810 g of water for injectable preparations into a dissolution vessel equipped with a cooling unit. The solution is cooled at a temperature of between 0 and 6.degree. C. throughout the manufacturing. 16.4 g of methanesulphonic acid are added and then 37.5 g of quinupristine, which are dissolved by mechanical stirring, and 87.5 g of dalfopristine, which are also dissolved by mechanical stirring, are successively introduced. The pH of the solution is adjusted to 4.75 by a 1N methanesulphonic acid solution. The solution is made up to 1 litre (1030 g) with water for injectable preparations.

Detailed Description Text (4):
This solution is sterilized by sterilized filtration (0.22 .mu.m) and divided up into bottles [500 mg of quinupristine/dalfopristine (30/70) per bottle] and then lyophilized [freezing: temperature-30.degree. C. to -50.degree. C.; freezing rate approximately 0.5.degree./min; sublimation: pressure 0.5 mbar; secondary desiccation: pressure (.apprxeq.30 .mu.bars) temperature 40.degree. C.].

Detailed Description Text (5):
The quality and the stability during storage of the lyophilisates or of the reconstituted solution are evaluated by a reverse-phase high performance liquid chromatography (HPLC) method which makes it possible to determine the content of dalfopristine and quinupristine and the content of degradation impurities.

Detailed Description Text (7):
The method of analysis by HPLC makes it possible to determine the contents of quinupristine and dalfopristine with an accuracy of 2% and the degradation

, impurities are determined to within about0.1%.

Detailed Description Text (8):
Two lyophilized batches of quinupristine/dalfopristine (30/70), composed of bottles containing 500 mg of active principle (batch 1a and batch 1b), were manufactured according to the above process and their stability studied at 4.degree. C. during storage for a period of 2 years. The results of the stability study on each of these 2 batches shows good preservation of the assays of the active principles and very little degradation (see Tables I and II).

Detailed Description Text (9):
Quinupristine/dalfopristine (30/70) solutions are reconstituted from these lyophilisates by taking up again in 5.0 ml of 5% glucose. Under these conditions, the stability of the concentrated solution thus constituted (premix), studied over a period of 60 minutes, is judged largely satisfactory for allowing subsequent dilution in an infusion bag (see Table III).

Detailed Description Text (10):
Under the dilution conditions anticipated for a clinical administration (500 mg of quinupristine/dalfopristine (30/70) in a 250 ml bag containing 5% glucose), the formulation ensures satisfactory stability over a period of at least 72 hours at 4.degree. C. or 6 hours at 25.degree. C. (see Tables IV and V).

Detailed Description Text (16):
Three batches of lyophilisates manufactured as described above (batch 1c, batch 1d, batch 1e) were used to test the stability of solutions diluted under clinical conditions (500 mg of lyophilized quinupristine/dalfopristine (30/70) diluted in 250 ml of 5% glucose).

Detailed Description Text (20):
125 mg/ml solutions of quinupristine/dalfopristine (30/70), at a pH of 4.50, salified either by hydrochloric acid or by methanesulphonic acid, are prepared according to the following protocol:

Detailed Description Text (21):
350 g of water for injectable preparations are introduced into a dissolution beaker. 30.0 g of quinupristine are dispersed in the water at room temperature using a mechanical stirrer. A 1N solution of methanesulphonic acid or of hydrochloric acid is added until dissolution is complete and a pH of 4.50 has been obtained. 70.0 g of dalfopristine are dispersed in the water using a mechanical stirrer and then a 1N solution of methanesulphonic acid or of hydrochloric acid is added until dissolution is complete and a pH of 4.50 has been obtained. Homogenization is carried out for 10 minutes.

Detailed Description Text (27):
125 mg/ml solutions of quinupristine/dalfopristine (30/70) are prepared respectively according to Example 1 or 2 at various pH values by addition of a variable amount of 1N methanesulphonic acid; these solutions are intended for lyophilization or for freezing. The pH of the solutions for lyophilization is fixed in a range of between 4.5 and 4.8. The pH of the solutions intended for freezing is fixed in a range of between 3.5 and 4.5.

Detailed Description Text (33):
Quinupristine/dalfopristine (30/70) solutions at a pH of 4.75 and at various concentrations of between 125 mg/ml and 250 mg/ml are prepared according to Example 1. These solutions are used to produce 500 mg lyophilisates. The most concentrated solutions (200 and 250 mg/ml) are slower to employ because of the time for dissolution of the dalfopristine and of the period of time for adjustment of the pH. The study shows that the degradation profiles during manufacture are not modified, only the times for redissolving lyophilisates are increased when the concentration of the solution is increased (see Table X).

Detailed Description Text (37):
125 mg/ml solutions of quinupristine/dalfopristine (30/70) are prepared according to Example 1 for which the adjustment of the pH to 4.75 is carried out by variable

amounts of 1N methanesulphonic acid (1 to 9 ml/1) and of 0.5N sodium hydroxide (0 to 15 ml/1).

Detailed Description Text (42):
Frozen quinupristine/dalfopristine (30/70) solutions, salified by methanesulphonic acid or by hydrochloric acid, are prepared in a concentration range of 5 and 20 mg/ml and at pH values of 3.5 and 5.0 and in the presence of isotonizing agents, such as NaCl and glucose. The stability of the solutions stored in the frozen form is judged satisfactory. (a) 800 g of water for injectable preparations are introduced into a dissolution vessel equipped with a cooling unit. The solution is cooled at a temperature of between 0 and 6.degree. C. throughout the manufacture. 98% of the amount of methanesulphonic acid necessary for the dissolution and for the adjustment of the pH are added. 1.5 g of quinupristine are introduced and dissolved with mechanical stirring. 3.5 g of dalfopristine are introduced and dissolved with mechanical stirring. The solution is isotonized with glucose. The pH of the solution is adjusted to 5.0 by a 0.1N solution of methanesulphonic acid. This solution is made up to 1 litre with water for injectable preparations.

Detailed Description Text (44):
(b) The preparation is carried out as described above but introducing 6 g of quinupristine and 14 g of dalfopristine. The pH of the solution is adjusted to 3.5 by a 0.1N solution of methanesulphonic acid. The solution is made up to 1 litre with water for injectable preparations.

Detailed Description Paragraph Table (2):
TABLE I 3
6 9 12 18 24 Batch 1a TO months months months months months months Assay (mg/bottle) Dalfopristine 350 347 343 343 345 358 342 Quinupristine 149 146 147 149 145 153 144 % impurities (A) 1.0 1.0 1.0 0.9 0.9 1.0 0.8 (B) 0.5 0.6 0.7 0.4 0.6 0.6 0.5 (C) 0.2 0.1 0.2 0.1 0.1 0.1 0.1 (D) 0.5 0.5 0.5 0.4 0.4 0.5 0.3 (E) 0.3 0.2 -- 0.1 0.2 0.1 0.1

Detailed Description Paragraph Table (3):
TABLE II 6 9 12 18 24 Batch 1b TO months months months months months Assay (mg/bottle) Dalfopristine 349 340 343 343 340 340 Quinupristine 148 144 146 142 143 142 % impurities (A) 1.0 0.8 0.8 0.9 0.9 0.8 (B) 0.5 0.6 0.4 0.6 0.4 0.5 (C) 0.2 0.2 0.1 0.2 0.1 0.2 (D) 0.4 0.4 0.4 0.4 0.4 0.3 (E) 0.1 -- 0.2 0.2 0.2 0.1

Detailed Description Paragraph Table (4):
TABLE III 15 30 45 60 Premix TO min min min min Assay (% with respect to TO) Dalfopristine 100.0 99.7 100.2 99.0 99.0 Quinupristine 100.0 100.2 100.7 99.6 101.1 % impurities (A) 0.74 0.89 1.02 1.12 1.28 (B) 0.51 0.62 0.69 0.72 0.78 (D) 0.47 0.49 0.46 0.53 0.61 Sum of the 0.28 0.30 0.32 0.33 0.38 other impurities

Detailed Description Paragraph Table (5):
TABLE IV Batch 1c Batch 1d Batch 1e Batches 72 h at 72 h at 72 h at tested TO 4.degree. C. TO 4.degree. C. TO 4.degree. C. (mg/250 ml) Dalfopristine 313 297 314 301 318 306 Quinupristine 135 127 134 129 136 131 % impurities (A) 1.5 4.2 1.1 4.1 1.6 4.5 (B) 0.7 0.9 0.6 0.8 0.8 1.0 (C) 0.2 0.3 0.1 0.3 0.2 0.3 (D) 0.3 0.4 0.4 0.5 0.4 0.4 (E) 0.3 0.3 0.2 0.2 0.6 0.3

Detailed Description Paragraph Table (6):
TABLE V
Batch 1c Batch 1d Batch 1e Batches 6 h at room 6 h at room 6 h at room tested TO temperature TO temperature TO temperature (mg/250 ml) Dalfopristine 314 304 321 311 319 313 Quinupristine 134 132 137 136 137 136 % impurities (A) 1.3 4.5 1.1 4.2 1.7 4.7 (B) 0.7 0.8 0.6 0.7 0.6 0.7 (C) 0.2 0.5 0.2

0.4 0.2 0.5 (D) 0.2 0.3 0.3 0.4 0.2 0.3 (E) 0.3 0.3 0.2 0.2 0.3 0.3

Detailed Description Paragraph Table (7):
TABLE VI
Methane- sulphonic 6 months 9 months 1 year acid TO 4.degree. C. R.T. 4.degree. C. R.T. 4.degree. C. R.T.
Assay (mg/bottle) 332 322 299 328 319 324 310 Dalfopristine 143 150 135 149 145 146 143 Quinupristine % impurities (A) 3.7 4.0 3.9 3.4 3.3 4.3 4.4 (B) 1.9 1.7 1.7 1.6 2.2 1.9 2.8 (C) 0.3 0.5 0.9 0.3 0.3 0.3 0.3 (D) 1.4 1.4 1.5 1.2 1.2 1.4 1.4

Detailed Description Paragraph Table (8):
TABLE VII 6 months Hydrochloric acid TO 4.degree. C. R.T. Assay (mg/bottle) Dalfopristine 327 333 313 Quinupristine 156 150 145 % impurities (A) 1.7 1.6 1.4 (B) 1.6 1.6 2.4 (C) 0.3 0.2 0.2 (D) 0.9 0.4 0.4

Detailed Description Paragraph Table (9):
TABLE VIII
Batch 3a Batch 3b Batch 3c* Batch 3d pH = 4.3 pH = 4.5 pH = 4.7 pH = 4.8 4 4 4 4 years years years years TO 4.degree. C. TO 4.degree. C. TO 4.degree. C. TO 4.degree. C.
Assay (mg/bottle) Quinupristine 175 148 159 154 152 153 159 149 Dalfopristine 384 291 343 313 331 321 351 328 % impurities (A) 0.6 0.5 0.6 0.8 0.8 0.9 1.1 1.1 (B) 1.0 3.3 0.8 2.1 0.9 1.2 1.0 1.1 (C) 0.5 0.5 0.4 0.4 0.4 0.4 0.3 0.5 (D) 0.8 0.7 0.9 0.6 0.7 0.6 0.8 0.5
*batch prepared with adjustment of the pH by addition of 6.5 ml of 0.5 N NaOH (under the conditions described below in Example 5).

Detailed Description Paragraph Table (10):
TABLE IX
Solution pH 3.5 Solution pH 4.0 Solution pH 4.5 Batch 3e Batch 3f Batch 3g (1) (2) (3) (1) (2) (3) (1) (2) (3)
Assay (mg/bottle) Quinupristine 147 148 152 147 153 148 144 136 144 Dalfopristine 339 328 335 320 336 331 334 313 334 % impurities (A) 2.0 1.9 2.0 1.8 1.8 2.0 2.6 3.3 3.6 (B) 0.9 1.1 1.3 1.0 1.0 1.6 1.0 1.5 1.7 (C) 0.3 0.3 0.3 0.3 0.4 0.4 0.2 0.4 0.2 (D) 0.9 1.0 1.1 1.1 1.0 1.0 1.4 1.4 1.4
(1):
After dissolution (2): After filtration (3): Before freezing

Detailed Description Paragraph Table (13):
TABLE XII
Batch 5b Batch 5d Batch 5f 4 months 1 month 3 months 4 months 1 month 3 months 4 months 1 month 3 months T0 30.degree. C. 30.degree. C. 30.degree. C. T0 4.degree. C. 30.degree. C. 30.degree. C. T0 4.degree. C. 30.degree. C. 30.degree.
C. Assay (mg/5 ml) Quinupristine Dalfopristine 154.4 153.5 153.6 156.5 152.8 153.3 151.4 150.8 146.3 146.2 144.1 143.0 361.4 364.4 358.9 354.8 358.7 359.6 353.2 345.7 345.9 347.1 340.7 336.4 % impurities (A) (B) 0.88 0.73 0.88 0.81 0.83 0.76 0.85 0.78 1.00 0.91 1.01 0.96 (C) 0.51 0.45 0.77 0.91 0.49 0.53 0.86 0.98 0.60 0.58 0.84 0.98 (D) 0.23 0.14 0.22 0.27 0.26 0.20 0.29 0.26 0.24 0.17 0.22 0.25 (E) 0.40 0.35 0.45 0.46 0.34 0.34 0.39 0.40 0.39 0.33 0.33 0.39 0.16 0.15 0.19 0.17 0.16 0.15 0.17 0.16 0.21 0.19 0.22 0.21

Detailed Description Paragraph Table (14):
TABLE XIII TO 3 months
Assay (mg/ml) Dalfopristine 3.37 3.38 Quinupristine 1.41 1.37 % impurities (A) 2.42 2.55 (B) 0.32 0.37 (C) 0.18 0.29 (D) 0.32 0.37 (E) -- 0.12

Detailed Description Paragraph Table (15):
TABLE XIV TO 3 months
Assay (mg/ml) Dalfopristine 14.0 16.8
Quinupristine 5.5 6.6 % impurities (A) 0.29 0.74 (B) 0.26 0.30 (C) 0.27 0.28 (D) 0.31 0.40

Detailed Description Paragraph Table (16):
TABLE XV TO 3 months
Assay (mg/ml) Dalfopristine 3.57 3.90
Quinupristine 1.42 1.57 % impurities (A) 0.25 0.56 (B) 0.20 0.21 (C) 0.21 0.15 (D) 0.30 0.35

Detailed Description Paragraph Table (17):
TABLE XVI TO 3 months
Assay (mg/ml) Dalfopristine 3.41 3.89
Quinupristine 1.45 1.63 % impurities (A) 2.77 2.64 (B) 0.32 0.35 (C) 0.21 0.15 (D) 0.32 0.37

CLAIMS:

1. A stabilized pharmaceutical composition comprising a pharmaceutically effective amount of quinupristine and dalfopristine, wherein said composition further comprises an at least stoichiometric amount, with respect to the total amount of dalfopristine and quinupristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid, and wherein said composition is physiochemically stable.

4. A stabilized pharmaceutical composition according to claim 1, wherein said pharmaceutically effective amount of quinupristine and dalfopristine is constant during the lifetime of said composition.

5. A stabilized pharmaceutical composition according to claim 1, wherein said quinupristine and said dalfopristine are present in a ratio of approximately 30:70.

7. A stabilized pharmaceutical composition according to claim 1, wherein said pharmaceutically effective amount of quinupristine and dalfopristine ranges from about 5 to about 250 mg/ml.

8. A stabilized pharmaceutical composition according to claim 1, wherein said pharmaceutically effective amount of quinupristine and dalfopristine is less than 5 mg/ml.

9. A stabilized pharmaceutical composition according to claim 6, wherein said pharmaceutically effective amount of quinupristine and dalfopristine in said lyophilizate ranges from about 5 to about 95%, by weight based upon the weight of the lyophilizate.

10. A stabilized pharmaceutical composition according to claim 9, wherein said pharmaceutically effective amount of quinupristine and dalfopristine in said lyophilizate ranges from about 20 to about 90%, by weight based upon the weight of the lyophilizate.

21. A process for preparing a stabilized pharmaceutical composition, said process comprising-simultaneously or successively introducing into water a pharmaceutically effective amount of quinupristine and dalfopristine and an at least stoichiometric amount, with respect to the total amount of quinupristine and dalfopristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid under conditions sufficient to achieve a stabilized pharmaceutical composition.

23. A process for preparing a stablized pharmaceutical composition according to claim 21, wherein said introducing into water is achieved by dissolving said pharmaceutically effective amount of quinupristine and dalfopristine in said water.

26. A process for preparing a stabilized pharmaceutical composition, said process

comprising successively introducing quinupristine and then dalfopristine into water acidified by at least one acid chosen from methanesulphonic acid and hydrochloric acid under conditions sufficient to achieve a stabilized pharmaceutical composition.

31. A process for preparing a stabilized pharmaceutical composition, said process comprising reconstituting a lyophilizate comprising a pharmaceutically effective amount of quinupristine and dalfopristine, wherein said composition further comprises an at least stoichiometric amount, with respect to the total amount of dalfopristine and quinupristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid, wherein said reconstituting step is carried out under conditions sufficient to provide a physiochemically stable pharmaceutical composition in any compatible and pharmaceutically acceptable injectable medium or infusion solution.

32. A process for preparing a stabilized pharmaceutical composition, said process comprising reconstituting a lyophilizate comprising a pharmaceutically effective amount of quinupristine and dalfopristine, wherein said composition further comprises an at least stoichiometric amount, with respect to the total amount of dalfopristine and quinupristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid, wherein said reconstituting step is carried out under conditions sufficient to provide a physiochemically stable pharmaceutical composition, and wherein said reconstituting step is carried out with a dilute solute having less than 20mg/ml of said quinupristine and dalfopristine.

33. A process for preparing a stabilized pharmaceutical composition, said process comprising defrosting a frozen composition comprising a pharmaceutically effective amount of quinupristine and dalfopristine, wherein said composition further comprises an at least stoichiometric amount, with respect to the total amount of dalfopristine and quinupristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid, wherein said defrosting step is carried out under-conditions sufficient to provide a physiochemically stable pharmaceutical composition.

34. A method for treating a bacterial infection, said method comprising administering to a patient in need thereof an effective amount of a stabilized pharmaceutical composition comprising a pharmaceutically effective amount of quinupristine and dalfopristine, wherein said composition further comprises an at least stoichiometric amount, with respect to the total amount of dalfopristine and quinupristine present in said composition, of at least one acid chosen from methanesulphonic acid and hydrochloric acid, and wherein said composition is physiochemically stable.

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L2: Entry 4 of 8 File: USPT Feb 13, 2001

DOCUMENT-IDENTIFIER: US 6187746 B1
TITLE: Pharmaceutical compositions based on dalfopristine and on quinupristine, and preparation thereof

Abstract Text (1):
The present invention relates to injectable compositions containing a dalfopristine/quinupristine combination comprising an aqueous solution containing the dalfopristine/quinopristine combination and an additive intended to avoid or reduce the intolerance effects at the site of injection.

Brief Summary Text (1):
The present invention relates to injectable antibacterial pharmaceutical compositions intended for the parenteral administration of quinupristine and dalfopristine, without entailing side effects of intolerance at the site of injection.

Brief Summary Text (4):
Quinupristine, a derivative of pristinamycin I, and dalfopristine, a derivative of pristinamycin II, are the components of Synercid.RTM.: ##STR3##

Brief Summary Text (5):
Synercid.RTM. (quinupristine/dalfopristine) is an injectable 30/70 combination whose antibacterial activity, in particular on vancomycin-resistant microorganisms is cited in many publications, e.g., The Annals of Pharmacotherapy, 29, 1022-1026 (1995); and Microbial Drug resistance, 1, 223-234 (1995).

Brief Summary Text (6):
Solubilization of the isolated components quinupristine or dalfopristine can be obtained in salt form. The preparation of stabilized pharmaceutical compositions comprising the quinupristine/dalfopristine combination proved to be very difficult and was finally achieved by adding at least stoichiometric amounts of methanesulphonic acid or hydrochloric acid, and were achieved at a pH within the range of from 3.5 to 5. These compositions also optionally contain a tonicity agent and/or other pharmaceutically acceptable adjuvants.

Brief Summary Text (7):
Attempts to prepare antibacterial pharmaceutical compositions comprising dalfopristine and quinupristine in the form of other salts have been unsuccessful due to the fact that one or both of the molecules was unstable either in solution or in lyophilized form.

Brief Summary Text (8):
The injection, in particular injection by infusion, of pharmaceutical compositions comprising the quinupristine/dalfopristine combination as described above entails venous intolerance effects localized in the region of the point of injection, which are manifested by inflammatory phenomena, phlebitis, allergic reactions or formation of oedemas which can go as far as to cause total interruption of the treatment. Such a situation is extremely troublesome since Synercid.RTM. (quinupristine/dalfopristine) currently proves to be among the only known clinical treatments for treating very serious infections caused by vancomycin-resistant microorganisms.

Brief Summary Text (11):
Furthermore, it has not been possible to prepare stable pharmaceutical compositions of the quinupristine/dalfopristine combination with citric acid or acetic acid.

Brief Summary Text (12):
It has now been found, and this forms the subject of the present invention, that the use of an additive, combined with the injection of the antibacterial pharmaceutical composition comprising the quinupristine/dalfopristine combination, can reduce, or even eliminate entirely, the localized side effects entailed by this combination of active principles. This occurrence is surprising, given the very different nature of each of the molecules combined and the difficulties associated with the instability of certain salts of one or the other of these molecules, e.g., the appearance of many degradation impurities, as well as the poor solubility and the instability of these active principles at certain pH values.

Brief Summary Text (13):
Thus, the additive has a protective role with respect to the venous intolerance effects entailed by the injection of the quinupristine/dalfopristine combination.

Brief Summary Text (14):
Formulations of the quinupristine/dalfopristine combination exist in liquid, lyophilized or frozen form.

Brief Summary Text (18):
The term additive is understood hereinabove to refer to a buffer solution chosen from any pharmaceutically acceptable aqueous solution buffered to acidic pH, capable of fixing the pH of the medium at a value below the pH of the blood plasma, and in particular at values at which the stability of the quinupristine/dalfopristine combination is not affected, i.e. at values which do not entail any immediate or rapid degradation of one and/or the other of the active principles. Preferably, the term additive is understood to refer to any pharmaceutically acceptable solution buffered to a pH ranging from 3 to 6.

Brief Summary Text (23):
According to the invention, the formulations of the quinupristine/dalfopristine combination, optionally reconstituted in the form of a concentrated solution (concentrate) or diluted, can be combined with a buffer solution at the time of injection. The combination can be made, indifferently, between the concentrate and the buffer solution (prediluted where necessary), before introduction into the infusion bag. The combination can also be made directly in the infusion bag, into which the buffer solution will have been introduced beforehand in order first to form a dilute buffer solution, followed by introduction of the concentrate. According to another alternative, the buffer solution can also be introduced into the bag already containing the active principle formulation. The combination can also be made using two infusion bags, one containing the active principle in the injectable medium and the other containing the dissolved buffer solution also in the injectable medium, the two bags being connected together by a Y-shaped catheter.

Brief Summary Text (28):
The stabilized antibacterial pharmaceutical compositions comprising the quinupristine/dalfopristine combination are prepared by simultaneous or successive dissolution of the quinupristine, dalfopristine, methanesulphonic acid or hydrochloric acid in water, followed by adjusting the pH with the range from 3.5 to 5 and/or addition of a tonicity agent and/or addition of other pharmaceutically acceptable adjuvants and, where appropriate, lyophilization and/or freezing.

Brief Summary Text (29):
The inventive compositions are more particularly prepared by dissolving the quinupristine component and subsequently the dalfopristine component in water that has been acidified with methanesulphonic acid or hydrochloric acid, followed, where appropriate, by adjusting the pH to within the range from 3.5 to 5 and/or addition of a tonicity agent and/or other pharmaceutically acceptable adjuvants. Where appropriate, they are lyophilized and/or frozen. The preparation and distribution of the solution are generally carried out between 0.degree. C. and room temperature, preferably at low temperature. This temperature depends on the duration of the

preparation and on the pH. The process is preferably performed at a temperature below 10.degree. C. These stabilized pharmaceutical compositions are optionally sterilized, in particular by sterilizing filtration.

Brief Summary Text (32):
These solutions may in addition contain one or more compatible and pharmaceutically acceptable adjuvants such as, for example, surface active agents. Among the surface active agents which can be used, there can be mentioned in a non-limiting manner polyoxyethylenated derivatives of oil of ricin, for example, cremophors; polyhydroxyethylated sorbitan esters, such as polysorbates, and in particular polysorbate 80; or lecithin. When such adjuvants are used in the buffer solution, these agents are introduced in such a manner that, in the final composition comprising the solution of active principle and buffer solution, they are present in a total quantity of from 1 to 25 mg per mg of the dalfopristine/quinopristine combination.

Brief Summary Text (33):
It is understood that the presentation kits for the formulation of the quinupristine/dalfopristine combination and for the additive also fall within the context of the present invention. Presentation kits of any form can be suitable, in particular, for example, presentations in the form of a twin-bottle, presentations in the form of an infusion bag containing the additive and bottle(s) containing the lyophilizate, presentations in the form of an infusion bag containing the active principle and a bottle or an ampoule containing the additive, and presentations involving one or more bottles comprising the lyophilizate and a bottle or an ampoule of the additive. Devices such as two-compartment syringes may also prove to be particularly suitable.

Detailed Description Text (3):
A bottle of Synercid.RTM. (70/30 dalfopristine/quinupristine combination) was reconstituted from 550 mg of lyophilizate of the 70/30 dalfopristine/quinupristine combination, by addition of 5 ml of water fip.

Detailed Description Text (10):
The dalfopristine/quinupristine lyophilizate was prepared in the following way:

Detailed Description Text (11):
One liter of a solution containing 125 mg/ml of quinupristine/dalfopristine (30/70), salified with methanesulphonic acid (z 16.7 mg/ml) to a pH of 4.75, was prepared by introducing 810 g of water for injectable preparation into a dissolution tank equipped with a refrigeration unit. The solution was refrigerated to a temperature that ranged from 0 to 6.degree. C. throughout the manufacture. 16.4 g of methanesulphonic acid were added, followed by successive introduction of 37.5 g of quinupristine, dissolved by mechanical stirring, and 87.5 g of dalfopristine, also dissolved by mechanical stirring. The pH of the solution was adjusted to 4.75 with 1N methanesulphonic acid solution. The solution was made up to 1 liter (1030 g) with water for injectable preparation.

Detailed Description Text (12):
This solution was sterilized by sterilizing filtration (0.22 .mu.m filter), distributed into bottles [500 mg of quinupristine/dalfopristine (30/70) per bottle] and then lyophilized [freezing: temperature -30.degree. C. to -50.degree. C.; freezing rate about 0.5.degree./min. Sublimation: pressure 0.5 mbar. Secondary desiccation: pressure (.apprxeq.30 .mu.bar) temperature 40.degree. C.].

Detailed Description Text (20):
The dose of 7.5 mg/kg of Synercid.RTM. (70/30 dalfopristine/quinupristine combination) taken up for 1 hour in a volume of 250 ml of aqueous 5% glucose solution corresponds to the unit dose used clinically via the i.v. route.

CLAIMS:

1. An injectable composition, said composition comprising an aqueous solution of dalfopristine and quinupristine, and an additive effective to avoid or reduce intolerance effects at the site of injection.

3. An injectable composition according to claim 1, wherein said additive is a pharmaceutically acceptable aqueous solution buffered to acidic pH, is capable of fixing the pH of the composition at a value below the pH of the blood plasma, and is capable of fixing the pH of the composition at a value at which the stability of the dalfopristine and quinupristine compounds is not affected.

15. A twin-compartment for preparing a solution for injection, said twin-compartment comprising a first compartment containing an aqueous solution of dalfopristine and quinupristine, and a second compartment containing an additive effective to avoid or reduce intolerance effects at the site of injection.

16. An injectable composition according to claim 1, wherein said aqueous solution of dalfopristine and quinupristine comprises methanesulphonic acid or hydrochloric acid in at least a stoichiometric amount relative to the total amount of dalfopristine and quinupristine present in said aqueous solution, and wherein the pH of said aqueous solution ranges from 3.5 to 5.

17. A method for protecting against venous intolerance effects caused by the injection of a composition containing quinupristine and dalfopristine, said method comprising adding to said composition prior to injection a buffer solution selected from any pharmaceutically acceptable aqueous solution that is buffered to an acid pH, that is capable of fixing the pH of the composition at a value below the pH of blood plasma, and that is capable of fixing the pH of the composition at a value that does not cause immediate or rapid degradation of the quinupristine, dalfopristine, or any other active component in the composition.

25. A kit, said kit comprising a first compartment containing an injectable composition comprising an aqueous solution of dalfopristine and quinupristine, and a second compartment containing an additive effective to avoid or reduce intolerance effects at the site of injection.

27. A kit according to claim 26, wherein said buffer solution is a pharmaceutically acceptable solution that is buffered to acidic pH, that is capable of fixing the pH of said injectable composition at a value below the pH of the blood plasma, and that is capable of fixing the pH of said injectable composition at a value at which the stability of the dalfopristine and quinupristine compounds is not affected.

28. A kit according to claim 25, further comprising methanesulphonic acid or hydrochloric acid, wherein said methanesulphonic acid or hydrochloric acid is added in at least a stoichiometric amount relative to the total amount of dalfopristine and quinupristine present in said injectable composition and wherein the pH of said composition ranges from 3.5 to 5.

29. A kit according to claim 25, said kit comprising a twin-bottle, an infusion bag containing said additive and at least one bottle containing a lyophilized formulation of quinupristine and dalfopristine, an infusion bag containing quinupristine and dalfopristine and a bottle or an ampoule containing said additive, at least one bottle containing a lyophilized formulation of quinupristine and dalfopristine and a bottle or an ampoule containing said additive, or a two-compartment syringe.

30. A method for treating a bacterial infection, said method comprising injecting into a patient an injectable composition according to claim 1 comprising an aqueous solution of dalfopristine and quinupristine, and an additive effective to avoid or reduce intolerance effects at the site of injection.

32. A method according to claim 30, wherein said additive is a pharmaceutically acceptable aqueous solution buffered to acidic pH, is capable of fixing the pH of the composition at a value below the pH of the blood plasma, and is capable of fixing the pH of the composition at a value at which the stability of the dalfopristine and quinupristine compounds is not affected.

35. A method according to claim 30, wherein said dalfopristine and quinupristine are present in said injectable composition in an amount such that from 5 to 15 mg/kg

thereof are injected into said patient.

36. A method according to claim 35, wherein said dalfopristine and quinupristine are present in said injectable composition in an amount such that from 5 to 7.5 mg/kg thereof are injected into said patient.

43. An injectable composition according to claim 16, further comprising methanesulphonic acid in at least a stoichiometric amount relative to the total amount of dalfopristine and quinupristine present in said composition.

44. A method for buffering an injectable composition comprising dalfopristine and quinupristine, said method comprising including in said injectable composition a pharmaceutically acceptable aqueous solution that is buffered to acidic pH, that is capable of fixing the pH of the composition at a value below the pH of the blood plasma, and that is capable of fixing the pH of the composition at a value at which the stability of the dalfopristine and quinupristine compounds is not affected, wherein said buffered aqueous solution protects the site of injection against venous intolerance effects caused by injection of a composition containing dalfopristine and quinupristine, and wherein the buffered injectable composition is an injectable composition according to claim 3.

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L2: Entry 3 of 8 File: USPT Oct 15, 2002

DOCUMENT-IDENTIFIER: US 6465428 B1
TITLE: Pharmaceutical combinations based on dalfopristine and quinupristine, and on cefepime

Abstract Text (1):
The present invention relates to pharmaceutical combinations of group A and group B streptogramins, in particular to combinations of dalfopristine and quinupristine, with cefepime, which combinations can exhibit a synergism of antibiotic action, to pharmaceutical compositions comprising the active ingredients, and to the bactericidal and bacteriostatic use of the combinations and compositions.

Brief Summary Text (1):
The present invention relates to combinations of quinupristine and dalfopristine with cefepime, which combinations can exhibit a synergism of action including bacteriostatic, as well as bactericidal, activity.

Brief Summary Text (2):
The present invention also relates to injectable pharmaceutical compositions intended for parenteral administration, which compositions comprise quinupristine and dalfopristine, in combination with cefepime.

Brief Summary Text (6):
Quinupristine, a derivative of pristinamycin I (a group B streptogramin), and dalfopristine, a derivative of pristinamycin II (a group A streptogramin), are the components of Synercid.RTM.: ##STR3##

Brief Summary Text (7):
Synercid.RTM. (quinupristine/dalfopristine) is an injectable 30/70 combination potent against most gram-positive pathogens, including methicillin resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus faecium (VREF). Its antibacterial activity is cited in many publications, including The Annals of Pharmacotherapy, 29, 1022-1026 (1995); Microbial Drug Resistance, 1, 223-234 (1995); and Antimicrobial Agents Chemother., 39, 1419-1424 (1995); etc.

Brief Summary Text (8):
International patent application WO 98/22107, the disclosure of which is specifically incorporated by reference herein, describes the preparation of stabilized pharmaceutical compositions comprising a quinupristine/dalfopristine combination, achieved in salt form, by adding at least stoichiometric amounts of methanesulphonic acid or of hydrochloric acid, and at a pH within the range of 3.5 to 5.0.

Brief Summary Text (9):
In the clinical environment, some bacteria, MRSA for instance, may jeopardize the efficacy of quinupristine/dalfopristine if adequate concentrations of dalfopristine are not present at the infection site. One way of circumventing this problem has been by increasing the number of doses of quinupristine/dalfopristine within a 24-hr period, or using a system of continuous infusion.

Brief Summary Text (11):
It has now been found, and this forms the subject of the present invention, that the combination of quinupristine/dalfopristine with cefepime can be of high interest in

the treatment of difficult-to-treat or life-threatening infections that require rapid bactericidal activity, as such combination can exhibit a synergy of action against such bacteria. The synergy results in a much higher potency which can, for instance, allow a decrease of the concentration of quinupristine/dalfopristine for administration or widen the dosing interval necessary to inhibit and to kill said bacteria, in particular against multi-drug resistant staphylococci, including methicillin-resistant strains.

Drawing Description Text (3):
FIG. 2 shows time-kill experiments using quinupristine/dalfopristine or cefepime alone or combined together.

Detailed Description Text (8):
For time-kill curves, series of flasks containing fresh prewarmed medium were inoculated with 10.sup.6 CFU/ml (final concentration) from an overnight culture of bacteria, and the bacteria were further incubated at 35.degree. C. with aeration at 120 rpm in a shaking incubator. Immediately after incubation, antibiotics were added to the flasks at final concentrations approximating the low levels of antibiotics produced in the serum of humans and rats by therapeutic doses of the drugs. Viable counts were determined just before and at various times after the addition of the antibiotics by plating adequate dilutions of the cultures on agar plates. To avoid antibiotic carryover, 0.5 ml samples of the structures were transferred from the flasks into microcentrifuge tubes, and the bacteria were spun and resuspended twice in antibiotic-free medium to remove residual drugs. Then the bacterial suspensions were serially diluted and spread on agar plates. When the .beta.-lactam drug (cefepime) was tested, the plates were supplemented with penicillinase as an additionnal precaution to avoid antibiotic carryover. Finally, due to the prolonged post antibiotic effect of quinupristine/dalfopristine, it was important to incubate the plates for at least 48 hours before the determination of viable counts. This avoided the false impression of quinupristine/dalfopristine-induced killing due to the delayed growth of surviving bacteria on the plate.

Detailed Description Text (10):
Sterile aortic vegetations were produced in female Wistar rats (weight 180 to 200 g) by the method of Heraiefet al., Infect Immunol., 37, 127-31 (1982), the disclosure of which is incorporated herein by reference in its entirety. Close by, an intravenous line containing a Silastic catheter was inserted into the jugular vein of a rat. The distal portion of the catheter was connected to a programmable pump device through a swivel, thus allowing the animals to move around their cage. The pump was set to deliver a volume of 0.2 ml of saline per hour to keep the line open until the onset of the therapy. In some experiments, quinupristine/dalfopristine was injected in combination with cefepime to the animals, with 2 infusion pumps, one to simulate human kinetics of quinupristine/dalfopristine and one to simulate human kinetics of cefepime. The 2 pumps were connected to a 2 way swivel and the drugs were infused into the animals via 2 independent jugular lines. No i.v. lines were placed in the control animals. Bacterial endocarditis was induced 24 hours after catheterization of the animals with 0.5 ml of saline containing 10.sup.5 CFU of either of the test organisms. This inoculum was 10 times larger than the minimum inoculum producing endocarditis in 90% of the untreated rats.

Detailed Description Text (12):
Treatment was started 12 hours after bacterial challenge and lasted 3 or 5 days. The distribution of the antibiotics simulated the drug kinetics in the serum of humans. Quinupristine/dalfopristine was given to simulate treatment in humans with 7 mg/kg of the drug administered i.v. every 12 hours. Cefepime was given to simulate treatment in humans with 2 g of the drug given i.v. every 12 hours. This required, for the experiment, a total amount (mg/kg of body weight) per 12 hours of 38 mg/kg of quinupristine/dalfopristine and 142 mg/kg of cefepime.

Detailed Description Text (16):
FIC Indexes of Quinupristine/dalfopristine Combined with Cefepime

Detailed Description Text (17):
Table 1 presents the ranges of MICs of the antibiotics for 10 MRSA isolates that were used to determine the FIC indexes. The FIC indexes demonstrated a positive

interaction between quinupristine/dalfopristine and cefepime on MRSA isolates.

Detailed Description Text (20):
Both MRSA AW7 and MRSA P8 were first exposed to quinupristine/dalfopristine or cefepime alone or combined together (FIG. 2, A and B). The drugs used alone were ineffective and failed to prevent bacteria growth. In contrast, when combined together, quinupristine/dalfopristine and cefepime blocked bacterial growth and even inflicted a reproducible loss of viability of 1-2 log.sub.10 CFU/ml after 24 hours of drug exposure. FIG. 2 shows time-kill experiments with AW7 (A) and P8 (B) exposed to concentrations of quinupristine/dalfopristine and/or cefepime, mimicking low antibiotic levels obtained during i.v. treatment in humans or in rats. Cultures received either no drug (diamonds), quinupristine/dalfopristine alone (squares), cefepime alone (triangles) or the combination of quinupristine/dalfopristine and cefepime (open circles). Low concentrations of quinupristine/dalfopristine and cefepime were 0.5 mg/l and 5 mg/l respectively.

Detailed Description Text (21):
Efficacy of Quinupristine/dalfopristine Alone or Combined with Cefepime in the Treatment of Experimental Endocarditis in Rats

Detailed Description Text (23):
The C-MLS.sub.B resistant MRSA: AW7 and P8, respectively, were tested further in animal studies. For these organisms, the MIC of quinupristine/dalfopristine was 0.5 mg/l and the MIC of cefepime was 64 mg/l.

Detailed Description Text (24):
For the model to be able to demonstrate synergy, in terms of bactericidal activity, when the drugs were to be combined, quinupristine/dalfopristine was given only at low doses (equivalent to 7.5 mg/kg i.v. every 12 hours (programmable pump)), in order to fail in monotherapy vs. the multi-resistant MRSA. Cefepime was given at 2 g i.v. every 12 hours.

Detailed Description Text (25):
Surprisingly, whereas monotherapy on C-MLS.sub.B resistant MRSA AW7 and P8 failed, in contrast, the combination gave a significant 5-6 log 10 decrease in the vegetation bacteria titers ($p<0.05$) after 5 days with the combination of quinupristine/dalfopristine and cefepime, when compared to both animals receiving single therapy and untreated controls.

Detailed Description Text (30):
In the above mentioned combinations, quinupristine/dalfopristine and cefepime can interestingly be used for treatment of humans in continuous injection or with shortened intervals between administrations. The doses of quinupristine/dalfopristine can be chosen in the range of from 10 to 30 or 60 mg/kg daily, in fractionated doses or continuous injection, and the doses of cefepime can be chosen in the range of from 1 to 4 or 8 g daily, in fractionated doses or continuous injection.

Detailed Description Text (32):
For the disclosed treatment, formulations of the quinupristine/dalfopristine can be presented in liquid, lyophilized or frozen form.

Detailed Description Text (35):
According to the invention, the formulations or compositions of quinupristine/dalfopristine, optionally reconstituted in the form of a concentrated solution (concentrate) or diluted, can be combined for coadministration with the cefepime solution at the time of injection. The combination can be made using 2 infusion bags, one containing quinupristine/dalfopristine in the injectable medium and the other containing the cefepime solution also in the injectable medium or using 2 syringes, one containing quinupristine/dalfopristine in the injectable medium, and the other containing the cefepime solution, or alternatively the combination can be made using one of the drugs in an infusion bag and the other in a syringe.

Detailed Description Text (36):

It is understood that the presentation kits for the formulation of quinupristine/dalfopristine and for the cefepime composition also fall within the context of the present invention. Presentation kits of any form can be suitable, in particular, for example, for presentations in the form of a twin-bottle, presentations in the form of an infusion bag containing quinupristine/dalfopristine and a bottle or an ampoule containing cefepime, presentations involving one or more bottles comprising quinupristine/dalfopristine and a bottle or an ampoule of cefepime. Devices such as two-compartment syringes may also prove to be particularly suitable.

Detailed Description Paragraph Table (1):
TABLE 1 Ranges of MICs of the antibiotics for MLS.sub.B -susceptible (susceptible to Macrolide Lincosanside-Streptogramin B - MLS.sub.B -S) and constitutively MLS.sub.B -resistant (Constitutively Resistant to Macrolide-Lincosamide-Streptogramin B-macrolide- and lincosamide-resistarit or C-MLS.sub.B -R) Staphylococcus aureus isolates also resistant to methicillin (MRSA *) Range of MICs (mg/l) MRSA MRSA Antibiotics MLS.sub.B -S C-MLS.sub.B -R Quinupristine/dalfopristine 0.25 0.25-0.5 cefepime >64 >64 * MRSA included 5 MLS.sub.B -susceptible and 5 C-MLS.sub.B -resistant clinical isolates

CLAIMS:

2. The synergistic antibiotic combination of claim 1, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

4. The pharmaceutical composition of claim 3, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

7. The presentation kit of claim 6,wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

9. The presentation kit of claim 8, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

11. The presentation kit of claim 10, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

13. The presentation kit of claim 12, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

19. The method of claim 15, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

20. The method of claim 16, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

22. The method of claim 21, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

24. The method of claim 23, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

26. The method of claim 25, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

28. The method of claim 27, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

30. The method of claim 29, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

32. The method of claim 31, wherein the group A streptogramin is dalfopristine and the group B streptogramin is quinupristine.

33. The method of claim 19, wherein the combination of dalfopristine and

quinupristine is present in an amount ranging from 10 to 60 mg/kg/day and the cefepime is present in an amount ranging from 1 to 8 g/day.

34. The method of claim 20, wherein the combination of dalfopristine and quinupristine is present in an amount ranging from 10 to 60 mg/kg/day and the cefepime is present in an amount ranging from 1 to 8 g/day.

37. The method of claim 33, wherein the combination of dalfopristine and quinupristine is present in an amount ranging from 10 to 30 mg/kg/day and the cefepime is present in an amount ranging from 1 to 8 g/day.

38. The method of claim 34, wherein the combination of dalfopristine and quinupristine is present in an amount ranging from 10 to 30 mg/kg/day and the cefepime is present in an amount ranging from 1 to 8 g/day.

57. The method of claim 19, wherein said administration comprises coadministration of said combination of dalfopristine and quinupristine and said cefepime at the same or different times.

58. The method of claim 20, wherein said administration comprises coadministration of said combination of dalfopristine and quinupristine and said cefepime at the same or different times.

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L2: Entry 7 of 8 File: EPAB May 28, 1998

PUB-NO: WO0009822107A1
DOCUMENT-IDENTIFIER: WO 9822107 A1
TITLE: STABILISED PHARMACEUTICAL COMPOSITIONS, WITH QUINUPRISTINE AND DALFOPRISTINE BASE AND THEIR PREPARATION

PUBN-DATE: May 28, 1998

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ABSTRACT:

CHG DATE=19980804 STATUS=O>The invention concerns a stabilised pharmaceutical composition, with a combined quinopristine/dalfopristine base, containing at least a stoichiometric amount of methanesulphonic acid or hydrochloric acid and is characterised in that its pH is included in the {3.5; 5} interval.